IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Bentwich et al.
App. No.:	10/536,560
Conf. No.:	9481
Filing Date:	December 20, 2005
Art Unit:	1635
Examiner:	SHIN, DANA H
Title:	BIOINFORMATICALLY DETECTABLE GROUP OF NOVEL VIRAL REGULATORY GENES AND USES THEREOF

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Dear Sir:

Appellant submits the following appeal brief to the Board of Patent Appeals and Interferences under 37 C.F.R. § 41.37. This appeal brief is filed in support of the Notice of Appeal filed on October 21, 2010, and in response to the final office action mailed on July 21, 2010 (the "Final Rejection" hereafter).

Claims 21-48 and 50-55 include all claims that were previously pending. Claims 21-34, 50, 52, and 53 are the claims currently under appeal.

I. REAL PARTY IN INTEREST

The real party in interest is Rosetta Genomics, Ltd., as indicated by the assignment in its name of the instant application recorded at reel/frame number 017640/0836.

II. RELATED APPEALS AND INTERFERENCES

Appellant is not aware of any prior or pending appeals, interferences, or judicial proceedings which may be related to, directly affect, or are directly affected by, or have a bearing on the Board's decision in this pending appeal.

III. STATUS OF CLAIMS

Claims 21-34, 50, 52, and 53 are pending and have been rejected. Claims 35-48, 51, 54, and 55 are pending and have been withdrawn. Claims 1-20 and 49 have been canceled. Appellant appeals the rejection of claims 21-34, 50, 52, and 53.

IV. STATUS OF AMENDMENTS

No amendment has been filed subsequent to the Final Rejection.

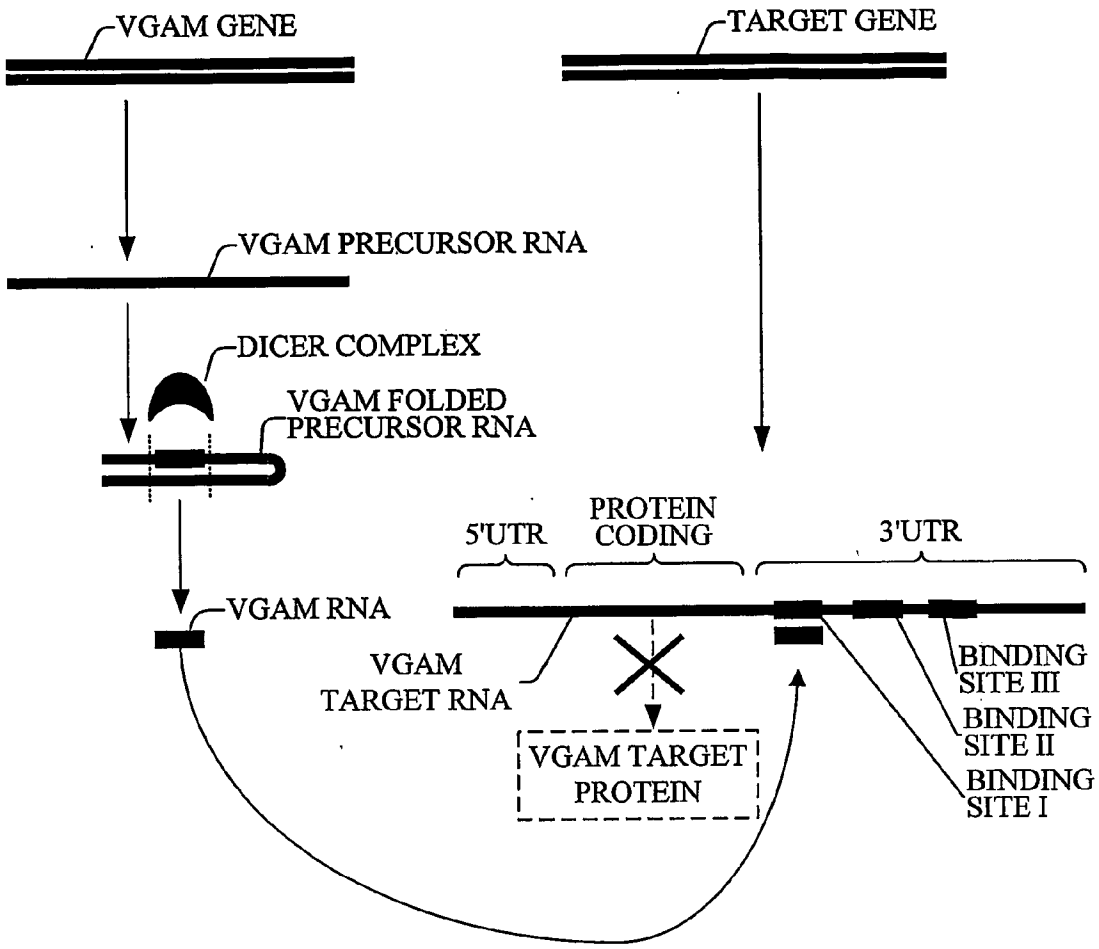
V. SUMMARY OF CLAIMED SUBJECT MATTER

Below is a concise explanation of the subject matter defined in claims 21, 33, and 34, which are the independent claims involved in this appeal, with references to the specification of this application (the "Instant Specification" hereafter) by page and line number, and to the drawings of this application.

A. Claim 21

Claim 21 relates to viral regulatory genes encoding microRNAs (miRNA), which repress expression of a target gene. ¶4 and 13. The application refers to a miRNA gene as a Viral Genomic Address Messenger or "VGAM." ¶2 and 4. Fig. 1 of the application (shown below) is a simplified diagram illustrating how the claimed miRNAs modulate expression of target genes. ¶40 and 65.

FIG. 1



The VGAM is contained in the virus genome. ¶67. The VGAM encodes a precursor RNA, which folds onto itself to form a hairpin structure due to complementary nucleotide sequences. ¶68-69. The enzymatic Dicer Complex cuts the folded hairpin precursor liberating the miRNA. ¶70. The miRNA binds to a binding site in the mRNA encoded by the target gene, thereby repressing expression of the target protein. ¶72.

The subject matter of claim 21 is directed towards viral miRNAs, which are referred to in the claim language as the "first viral nucleic acid." The claimed group of miRNAs are identified as being 15-24 nucleotides in length[1]. The claimed miRNAs are also capable of binding to a binding

[1] *See* Instant Application at Table 3 (disclosing a total of 1797 miRNAs, each of which has a length in this range).

site of a mRNA[2], and capable of inhibiting expression of a protein encoded by a mRNA that comprises the binding site.[3]

The claimed group of miRNAs (or first viral nucleic acids) are also identified by reference to the precursor RNAs, which are referred to as a "second viral nucleic acid." As shown above in Figure 1 of the application, the sequence of the miRNA (or first viral nucleic acid) is contained within the precursor RNA (or second viral nucleic acid). As also shown above, the sequence of the miRNA (or first viral nucleic acid) and the sequence of the precursor RNA (or second viral nucleic acid) are both contained within a viral genome.[4]

The precursor RNAs (or second viral nucleic acids) are 50 to 131 nucleotides in length.[5][6] The two stem segments of the folded precursor RNA (or second viral nucleic acid) are 14-71 nucleotides in length and contain a loop segment of 3 to 19 nucleotides.[7] The first and second stem segments of the precursor RNAs (or second viral nucleic acids) are at least 30.8% complementary.[8] The sequence of the miRNA (or first viral nucleic acid) is contained within one of the stem segment of the hairpin precursor (or second viral nucleic acids).[9]

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[2] *See* Instant Specification at page 4, line 29 (disclosing that, "…a nucleotide sequence of the RNA encoded by the novel viral gene is a partial inversed-reversed sequence of a nucleotide sequence of a binding site associated with at least one host target gene…").

[3] *See* Instant Specification at page 6, line 1 (disclosing that, "…the RNA encoded by the novel viral gene complementarily binds the binding associated with the at least one target host gene, thereby modulating expression of the at least one target host gene").

[4] *See* Instant Specification at page 1, line 6 (disclosing that, "[t]he present invention relates to a group of bioinformatically detectable novel viral genes…").

[5] *See* Instant Specification at page 4, line 29 (disclosing that, "RNA precursor is about 50 to about 120 nucleotides in length…") *and see also* Instant Application at SEQ ID NO: 4 of the Sequence Listing *and* at Table 2, lines 253-261 (disclosing a viral hairpin that is 131 nucleotides in length).

[6] *See* Instant Specification at page 4, line 29 (disclosing that, "a nucleotide sequence of a first half of the RNA precursor is a partial inversed-reversed sequence of a nucleotide sequence of a second half thereof…").

[7] *See* Instant Application at Table 2 (showing diagrams depicting stem-loop structures of the claimed nucleic acids, and disclosing 1593 stem-loop structures that have a length between 14 and 71 nucleotides and that a loop segment between 3 and 19 nucleotides) *and see also* Instant Application at SEQ ID NO: 867 (which as disclosed in Table 2 has stem segment of 19 nucleotides) *and* at SEQ ID NO: 251 (which as disclosed in Table 2 has a stem segment of 71 nucleotides) *and* at SEQ ID NO: 625 (which as disclosed in Table 2 has a loop of 3 nucleotides) *and* at SEQ ID NO: 1302 (which as disclosed in Table 2 has a loop of 19 nucleotides).

[8] *See* Instant Application at Table 2, lines 4402-4406 (showing 30.8% complementarity percentage between first and second segments of a hairpin, which is the minimum complementarity disclosed in Table 2).

[9] *See* Instant Specification at page 4, line 29 (disclosing that, "…RNA encoded by the bioinformatically detectable novel viral gene is about 18 to about 24 nucleotides in length, and originates from an RNA precursor…").

B. Claim 33

Claim 33 relates to a probe comprising the nucleic acid of claim 21 (as well as any one of those of claims 22-32).[10]

C. Claim 34

Claim 34 relates to a vector comprising the nucleic acid of claim 21 (as well as any one of those of claims 22-32).[11]

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether claims 21-34, 50, 52, and 53 are unpatentable under 35 U.S.C. § 112, second paragraph.
2. Whether claims 21, 22, 33, 34, 50, and 52 are unpatentable under 35 U.S.C. § 102 over Khvorova, Usman, Stacey, Berlin, Baker, and Lieven.
3. Whether claims 21, 52, and 53 are unpatentable under 35 U.S.C. § 102 over Zhu, Ghiringhelli, Baumstark, Ozdarendeli, and Davison.
4. Whether claims 21-34, 50, 52, and 53 are unpatentable under 35 U.S.C. § 103 over Lai, Zhu, Ghiringhelli, Baumstark, Ozdarendeli, Davison, and Perry.
5. Whether claims 21, 33-34, 52 and 53 are unpatentable on grounds of nonstatutory obviousness-type double patenting over U.S. Patent Nos. 7,696,334, 7,790,867, 7,696,342, 7,759,478 and 7,217,807; and U.S. Patent Appl. Nos. 10/709,739, 11/511,035 and 12/517,760.

VII. ARGUMENT

A. Claims 21-34, 50, 52, and 53 are not indefinite under 37 C.F.R. § 112, second paragraph because the claimed nucleic acids are properly limited by reference to precursors

Claims 21-34, 50, 52, and 53 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Claim 21 is representative of this set of claims, and it relates to viral miRNAs.

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[10] *See* Instant Specification at page 6, one 22 (disclosing that, "…the invention includes a probe including the DNA").

[11] *See* Instant Specification at page 6, line 11 (disclosing that, "…invention includes a vector including the DNA").

At the time of filing, miRNA genes were known to be present only in the genomes of complex eukaryotic (*i.e.*, multicellular) organisms. Appellant's pioneering discovery was that primitive viruses, which are acellular (*i.e.*, have no cells), also harbor miRNA genes in their genomes. As shown in Figure 1, the miRNA genes encodes a precursor RNA that folds to form a hairpin structure. The folded hairpin precursor is cut by the Dicer Complex to yield a miRNA of 15-24 nucleotides in length. The miRNA represses expression of a target protein by binding to a binding site in the target mRNA.

The subject matter of claim 21 is related to viral miRNAs, which are referred to in the claim language as the "first viral nucleic acid." The scope of claim 21 is limited by reference to structural and functional features of the claimed nucleic acids. For example, the claimed nucleic acids are 15-24 nucleotides in length (element "a" of claim 21), capable of binding to a binding site of a mRNA (element "d" of claim 21) and also capable of inhibiting expression of a protein encoded by the mRNA comprising the binding site (element "e" of claim 21). These claim elements are not in dispute.

The nucleic acids of claim 21 are also limited by reference to precursor RNAs, which are referred to as the "second viral nucleic acid." Specifically, the claims require that the second viral nucleic acid comprise the first viral nucleic acid (element "b"). In other words, the first viral nucleic acid is found within the second viral nucleic acid. This property is clearly shown in Figure 1 and discussed at length in the specification. The second viral nucleic acid is described by its length (50-131 nucleotides in element "b") and also the hairpin structure (element "c").

As correctly noted by the Examiner, claim 21 is drawn to the first nucleic acid not to the second nucleic acid. The Examiner alleges, however, that the recitation of structural limitations for the second nucleic acid does not do anything to limit the scope of the first nucleic acid, and therefore, renders claim 21 indefinite. Appellant respectfully disagrees, because it is permissible for claimed subject matter to be limited by reference to unclaimed subject matter.

In *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565 (Fed. Cir. 1986), the claim at issue was held not to be indefinite under 35 U.S.C. § 112, second paragraph, despite being limited by reference to unclaimed subject matter. The claim at issue in *Orthokinetics* was directed to a wheel chair, which was limited by reference to something other than the wheel chair itself. Specifically, the wheel chair had a front leg portion that was limited by reference to a car into which the wheel chair was intended to fit. In particular, the front leg portion was, "…so dimensioned as to be insertable

through the space between the doorframe of an automobile and one of the seats thereof…"[12] Thus, although the subject matter of the claim in *Orthokinetics* related only to the wheel chair, the size of part of the wheel chair was limited by the size of a car doorframe—a doorframe that was not claimed.

Upon review of whether the claim met the requirements of definiteness under § 112, 2d paragraph, the Federal Circuit held that the only relevant consideration was whether, "those skilled in the art would understand what is claimed when the claim is read in light of the specification."[13] In *Orthokinetics*, there was ample evidence that one of ordinary skill in the art could easily have determined the appropriate dimensions of the front leg of the wheel chair based on what was known about car doors.[14] Consequently, the Federal Circuit stated, "[t]hat a particular chair on which the claims read may fit within some automobiles and not others is of no moment…. As long as those of ordinary skill in the art realized that the dimensions could be easily obtained, § 112, 2d para. requires nothing more."[15]

Appellant's limiting of the claimed first viral nucleic acid by reference to the second viral nucleic acid is no different from the wheel chair in *Orthokinetics* having been limited by reference to the dimensions between a car doorfame and the car seat. The only consideration in this case is whether one of ordinary skill in the art could determine the requirements of the second nucleic acid. Appellant submits that this is certainly the case.

Given any nucleic acid sequence of interest, one of skill need only compare that sequence to the sequences of viral genomes. If the nucleic acid of interest is not contained in a viral genome, that is the end of the matter, because that means that the nucleic acid of interest unequivocally falls outside the scope of claim 21. Moreover, it should be noted the sequence of viral genomes are readily accessible to one of ordinary skill in the art. At least 85 virus genomes were reported at the time the application was filed. In addition, much more complex genomes of numerous multicellular organisms had been sequenced at the time of filing.

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[12] *Orthokinetics*, 806 F.2d at 1568.

[13] *Orthokinetics*, 806 F.2d at 1576.

[14] *See Orthokinetics*, 806 F.2d at 1576 ("…witnesses, who were skilled in the art, testified that such a task [measuring the space between a selected automobile's door frame and its seat and making the wheel chair to fit in this space] is evident from the specification and that one of ordinary skill in the art would easily have been able to determine the appropriate dimensions").

[15] *Orthokinetics*, 806 F.2d at 1576 (emphasis added).

If the nucleic acid of interest is contained in a viral genome, then one of skill need only identify the window of genomic sequence segments in viral genomes containing the nucleic acid of interest that are 50-131 nucleotides in length. This group of sequences is then reviewed to determine whether a hairpin can formed that has two stem segments and an intervening loop segment, where each stem segment consists of 14-71 nucleotides, where the loop segment consists of 3-19 nucleotides, and where the first and second stem segments are at least 30.8% complementary (*i.e.*, identify all of the second viral nucleic acids contained in viral genomes). In other words, one of skill would only need to identify all of the hairpin-forming segments with a defined length and a defined structure that are contained in viral genomes. One of ordinary skill in the art could readily identify all such hairpin-forming sequence segments; methods for doing so are described throughout the instant specification. Once identified, one of ordinary skill in the art need only determine whether the nucleic acid of interest is contained in one of the stem segments of the hairpins. If the nucleic acid of interest is not contained in the one of the stem segments, then the nucleic acid unequivocally falls outside the scope of claim 21.

In contrast, if the nucleic acid of interest is contained in one of the stem segments, the nucleic acid falls in the scope of claim 21 only if the nucleic acid is capable of binding to a binding site of a mRNA, and of inhibiting expression of a protein encoded by a mRNA that comprises the binding site. Again, one of ordinary skill in the art could readily make these determinations. And because all of the steps for determining whether a nucleic acid of interest falls within the scope of claim 21 could have readily have been performed by one of ordinary skill in the art at the time of filing, claim 21 is not indefinite simply because it refers to the second viral nucleic acid to limit the scope of the claimed first viral nucleic acid. Accordingly, claim 21, and consequently claims 22-34, 50, 52, and 53, are not indefinite. In view of the foregoing, Appellant respectfully requests that the rejection of claims 21-34-50, 52, and 53 under 35 U.S.C. § 112, second paragraph, be withdrawn.

B. Claims 21-34, 50, 52, and 53 are entitled to benefit from the filing date of earlier-filed priority applications because the priority applications provide sufficient written description support under 35 U.S.C. § 112, first paragraph for the instantly claimed subject matter

The instant claims have been denied the benefit of earlier-filed applications to which the instant application claims priority. In particular, the instant application claims priority to earlier-filed applications as indicated in the following table.

Relationship to earlier-filed application	Earlier-filed priority application number	Filing date
This application is National Stage Entry of	PCT/IL03/00998	11/26/2003
is a Continuation-in-part of	10/605,840	10/30/2003
is a Continuation-in-part of	10/605,838	10/30/2003
is a Continuation-in-part of	10/604,984	8/29/2003
is a Continuation-in-part of	10/604,944	8/28/2003
is a continuation of	10/604,944	8/28/2003
is a Continuation-in-part of	10/604,943	8/28/2003
is a Continuation-in-part of	10/604,942	8/28/2003
is a Continuation-in-part of	10/604,945	8/27/2003
Claims Priority from Provisional Application	60/457,788	3/27/2003
Claims Priority from Provisional Application	60/441,241	1/17/2003
is a Continuation-in-part of	10/310,188	12/5/2002
is a continuation of	10/310,188	12/5/2002
is a Continuation-in-part of	10/308,778	12/3/2002
is a continuation of	10/303,778	11/26/2002
is a Continuation-in-part of	10/303,778	11/26/2002
Claims Priority from Provisional Application	60/411,230	9/17/2002
is a Division of	09/522,872	3/10/2000
Claims Priority from Provisional Application	60/123,833	3/11/1999

Each of the afore-mentioned priority applications discloses thousands of viral nucleic acids, both miRNAs and mRNA hairpin precursors. These nucleic acids are disclosed in tables, like in the instant application, and in sequence listings. Looking at any one of these applications on its own, one of skill would recognize that the disclosed nucleic acids, when viewed as a whole, describe viral miRNAs and miRNA precursors with the characteristics of those of the instant claims.

Nevertheless, the Examiner has denied the instant claims the benefit of any earlier-filed priority application. In particular, the Examiner asserts that the instant claims lack sufficient written description support in the priority applications, because the earlier-filed applications do not explicitly provide written description support for viral nucleic acids that have the same structures as those of the instant claims. In particular, the Examiner alleges a lack of support in the priority applications for limitations such as SEQ ID NO: 2079, "15-24 nucleotides," "50-131 nucleotides," "14-71 nucleotides," "3-19 nucleotides," "18-24 nucleotides," "50-120 nucleotides," "intervening loop," "30.8% complementarity," "40.9% complementarity," and the like.

The Examiner, however, overlooks the fact that the disclosure of viral miRNA precursor hairpins and miRNAs by an earlier-filed application must be viewed as a whole in order to properly assess whether the instant claims find sufficient written description support in the earlier-filed application. Thus, what is critical is not whether the limitations of the instant claims are explicitly

recited in a earlier-filed priority application, but whether the limitations find support in the group of miRNA hairpin precursors disclosed in the priority application as a whole. Had the Examiner properly looked at the viral nucleic acids disclosed by the earlier-filed applications as a whole, it would have been apparent that viral nucleic acids with structures like those of the instant claims are disclosed. Because the priority applications disclose groups of miRNA precursor hairpins and miRNAs that, when assessed in their totalities, have the characteristics of the instantly claimed nucleic acids, the instantly claimed subject matter is entitled to the effective filing date of the priority applications. In addition, Appellant submits that the decision to grant or deny the instant claims the benefit to an effective filing date earlier than the filing date of the instant application does not affect Appellant's arguments herein regarding the patentability of the instant claims under 35 U.S.C. §§ 102, 103, and 112.

C. Claims 21, 22, 33, 34, 50, 52, and 53 are not anticipated by the cited art under 35 U.S.C. § 102 because none of the cited references discloses all of the claim limitations

Claims 21, 22, 33, 34, 50, 52, and 53 stand rejected under 35 U.S.C. § 102 as allegedly being anticipated by U.S. Patent Application Publication No. 2007/0031844 ("Khvorova"; claims 21, 22, 33, 34, 50, 52 under 35 U.S.C. § 102(e)); U.S. Patent Publication Publication No. 2005/0124568 ("Usman"; claims 21, 22, 33, 34, 50, and 52 under 35 U.S.C. § 102(e)); International Patent Publication No. WO/00/31540 ("Stacey"; claims 21, 22, 33, 34, 50, and 52 under 35 U.S.C. § 102(b)); International Patent Publication No. WO/02/77272 ("Berlin"; claims 21, 22, 33, 50, and 52 under 35 U.S.C. § 102(b)); U.S. Patent No. 6,399,297 ("Baker"; claims 21, 22, 33, 34, 50, and 52 under 35 U.S.C. § 102(b)); U.S. Patent No. 6,087,093 ("Lieven"; claims 21, 22, 33, 50, and 52 under 35 U.S.C. § 102(b)); Zhu *et al.* (Journal of General Virology, 1992;73:1309-12) ("Zhu"; claims 21 and 52 under 35 U.S.C. § 102(b)); Ghringhelli *et al.* (Journal of General Virology, 1991;72:2129-41) ("Ghringhelli"; claims 21 and 52 under 35 U.S.C. § 102(b)); Baumstark *et al.* (RNA, 2001;7:1652-70) ("Baumstark"; claims 21 and 52 under 35 U.S.C. § 102(b)); Ozdarendeli *et al.* (Journal of General Virology, 2001;75:7362-74) ("Ozdarendeli"; claims 21, 52, and 53 under 35 U.S.C. § 102(b)); and by Davison *et al.* (Journal of General Virology, 1985;66:207-20) ("Davison"; claims 21, 52, and 53 under 35 U.S.C. § 102(b)). Claim 21 is representative of the claims rejected under 35 U.S.C. § 102.

Appellant asserts that none of these references discloses all of the limitations of the instant claims.[16] The references cited by the Examiner fall into two broad categories. In one, the references do not disclose a nucleic acid that is "viral," which is required by the pending claims. The references Khvorova, Usman, Stacey, Berlin, Baker, and Lieven fall into this first category (the "Non-Viral References"). In the other category, the references fail to disclose a viral nucleic acid that falls within certain length requirements. Specifically, the claimed nucleic acids must be 15 to 24 nucleotides. The references Zhu, Ghiringhelli, Baumstark, Ozdarendeli, and Davison fall into this second category (the "Large References").

1. The Non-Viral References do not anticipate the instant claims because these references do not disclose all of the limitations of the instant claims

In the rejections based on the Non-Viral References, the Examiner completely ignores the fact that the instantly claimed nucleic acid is "viral." Specifically, the claims require that a viral genome comprise the sequence of the claimed nucleic acid. In other words, the sequence of the claimed nucleic acids must also be found in the genome of a virus. Instead, for purpose of examination, the Examiner mistakenly construed the "viral" limitation of the instant claims to encompass a sequence that is at least 30.8% complementary to the claimed nucleic acid. Such a construction mistakenly broadens the scope of the claims to include nucleic acids from other organisms as well as synthetic, non-natural nucleic acids. This interpretation of the claims by the Examiner is clearly erroneous.

Specifically, claim 21 explicitly claims, "[a]n isolated first **viral** nucleic acid."[17] Additionally, and importantly, claim 21 explicitly recites that "**a viral genome comprises the sequence of the first and second viral nucleic acids**."[18] Accordingly, a prior art nucleic acid does not anticipate the instantly claimed nucleic acid by being "essentially identical" to the instantly claimed nucleic acid, because being "essentially identical" to the instantly claimed nucleic acid does not make a cited prior art nucleic acid inherently viral. Instead, in order to anticipate the instant claims the sequence of the prior art nucleic acid **must be present in the genome of a virus**. That is, the prior art nucleic acid must be 100% identical to a sequence found within a virus genome. The Examiner fails to establish

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[16] See MPEP § 2131 *quoting Verdegaal Bros. v. Union Oil Co. of Calif.*, 814 F.2d 628 (Fed. Cir. 1987) ("'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference'").

[17] Instant claim 21 (emphasis added).

[18] Instant claim 21 (emphasis added).

that any one of the cited nucleic acids from the Non-Viral References is 100% identical to a sequence from a viral genome. The Examiner is unable to make this showing because not a single one of the cited nucleic acids from the Non-Viral References is found in any known viral genome. Instead, each of the cited nucleic acids from the Non-Viral References is synthetic (i.e., not naturally occurring). A non-natural nucleic acid is clearly outside the scope of the claims.

2. The Large References do not anticipate the instant claims because these references do not disclose all of the limitations of the instant claims

In the rejections based on the Large References, the Examiner completely ignores the fact that the instantly claimed first viral nucleic acid must not only be isolated, but must also **consist** of 15-24 nucleotides. None of the cited nucleic acids from the Large References teaches or suggests nucleic acids possessing a length within the required limitation of 15-24 nucleotides.

Instead, each of the cited nucleic acids from the Large References exceeds the length limitation of the instantly claimed nucleic acid. In particular, the cited nucleic acids disclosed in Zhu, Ghiringhelli, Baumstark, Ozdarendeli, and Davison are 138,[19] 121,[20] 41 to 63,[21] 138,[22] and 48[23] nucleotides in length, respectively. Thus, not one of the cited nucleic acids from the Large References consists of 15-24 nucleotides. The Examiner's assertion that a sequence that is longer than 24 nucleotides in length inherently possesses an isolated nucleic acid that is shorter[24] is of no avail. The term, "consisting of," "excludes any element, step, or ingredient not specified in the claim."[25] Accordingly, because the cited nucleic acids from the Large References are longer than 24 nucleotides, they include elements that are excluded from the instant claims. Furthermore, none of the Large References teaches or suggests fragments of the nucleic acids cited by the Examiner. Since the Large References do not teach or suggest an isolated nucleic acid consisting of 15-24

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[19] *See* Zhu at Fig. 2.

[20] *See* Ghiringhelli at Fig. 6.

[21] *See* Baumstark at Fig. 7B.

[22] *See* Ozdarendeli at Fig. 2A.

[23] *See* Davison at Fig. 6.

[24] *See, e.g.*, Final Rejection at page 12, line 14 ("Contrary to Appellant's argument, the nucleic acid isolated from nucleotides 1010-1055 (see Figure 2) of RSV-T RNA 4 of Zhu et al. inherently possesses an "isolated" nucleic acid that is 21 nucleotides in length and its complement thereof…").

[25] MPEP § 2111.03 *citing In re Gray*, 53 F.2d 520 (CCPA 1931) *and Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948).

nucleotides, these references do not disclose all of the limitations of the instantly claimed subject matter and therefore do not anticipate the instant claims.

In view of the foregoing, Appellant respectfully submits that the rejection of claims 21, 22, 33, 34, 50, 52, and 53 under 35 U.S.C. § 102 has been overcome and should be withdrawn.

D. Claims 21-34, 50, 52, and 53 are not obvious over cited art under 35 U.S.C. § 103 because one of ordinary skill in the art did not have a reasonable expectation of success that combining and modifying the teachings of the cited references would have led one ordinary skill in the art to arrive at the claimed subject matter

Claims 21-34, 50, 52, and 53 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lai *et al.* (Genome Biology, 2003;4:1-20) ("Lai") in view of Zhu, Ghiringhelli, Baumstark, Ozdarendeli, Davison, and Perry *et al.* (Journal of General Virology, 1988;69:2831-46) ("Perry"). The Examiner asserts that Lai discloses a computational, bioinformatics-based approach to discovering unknown miRNAs in a given sequenced genome. Critically, the Examiner fully admits that Lai teaches nothing about being able to identify miRNAs in a genome.[26] Zhu, Ghiringhelli, Baumstark, Ozdarendeli, and Davison are all cited as allegedly disclosing that non-coding regions of viral genomes can contain hairpin structures that appear to have a structure "similar" to miRNA hairpin precursors. The structures cited by the Examiner may be hairpins, but they are not miRNA hairpin precursors because they do not possess the claimed characteristics.

The Examiner cites Perry as allegedly disclosing the sequence of the entire human simplex virus 1 ("HSV-1") genome. Like Zhu, Ghiringhelli, Baumstark, Ozdarendeli, and Davison, however, Perry teaches nothing about viral miRNAs, or the ability to discover viral miRNAs in the HSV-1 genome. The HSV-1 genome indeed contains non-coding, intergenic sequences that encode miRNAs, but this was known only after Appellant's discovery, and the filing of the instant application. Nevertheless, the Examiner asserts that because viral genomes were known to contain hairpins at the time the instant application was filed, it would have been obvious to one of skill in the art to use a computer algorithm like Lai's to identify potential miRNAs in non-coding regions of viral genomes such as that disclosed by Perry, and thereby arrive at the instantly claimed subject matter. Applicant respectfully submits that this is clearly erroneous.

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[26] *See* Final Rejection at page 17, line 8 ("Lai et al. do not teach miRNAs identified in a viral genome using their bioinformatics-based 'miRseeker' program").

The issue here is not simply whether one of ordinary skill in the art would reasonably expect the genome of a virus to contain hairpin structure in general, but rather **whether one of ordinary skill in the art would reasonably have expected a virus genome to contain the very specific structure of a miRNA hairpin precursor**. Applicant submits that the Examiner has failed to establish that such a reasonable expectation existed at the time of filing. The evidence, when considered as a whole, clearly shows there to be an inventive leap from miRNAs in complex eukaryotic genomes to the predictability of primitive virus genomes containing miRNAs.

Appellant submits that this conclusion is necessitated when the proper standard of obviousness is applied to Appellant's evidence. The evidentiary standard for obviousness is articulated in MPEP § 2142, which states the following (emphasis added):

> ***If the examiner determines there is factual support for rejecting the claimed invention under 35 U.S.C. 103, the examiner must then consider any evidence supporting the patentability of the claimed invention, such as any evidence in the specification or any other evidence submitted by the Appellant. The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. In re Oetiker, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). The legal standard of "a preponderance of evidence" requires the evidence to be more convincing than the evidence which is offered in opposition to it. With regard to rejections under 35 U.S.C. 103, the examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e., the reference teachings establish a prima facie case of obviousness) is more probable than not.***

The Examiner must weigh the Appellant's evidence presented on the record under a preponderance standard rather than an absolute standard for deciding whether there was a lack of predictability in the art at the time of filing that one of skill would not have expected to succeed in identifying viral miRNAs.

The evidence that the Appellant has presented on the record includes, in part, that (1) at the time of filing, miRNAs and miRNA hairpin precursors were believed to be present in only complex eukaryotes; (2) algorithms such as those taught in Lai for predicting secondary structures such as hairpin precursors were based upon hairpins and miRNAs that had solely been identified in higher eukaryotic organisms; and (3) viral genomes are too small and have too little intergenic space to have expected RNA hairpin precursors to be present in view of the known miRNA hairpin precursor frequency in divergent plant and eukaryotic organisms.

Under a proper analysis, therefore, the Examiner must consider that all the prior art miRNA sequences at the time of filing were known **only** from complex, evolutionarily-related organisms that are grouped among a few branches of the phylogenic tree.[27] One of ordinary skill in the art would therefore have predicted that the shared existence miRNAs among these evolutionarily-related organisms arose as a result of the conservation of genome sequences among these organisms due to their common ancestry. In fact, the computational method of Lai cited by the Examiner relies on this sequence conservation for identifying additional miRNAs. Consequently, Lai's miRNA search algorithm is based on miRNA sequences that are conserved across bilaterian organisms, and is therefore only applicable to higher multicellar organism such as worms, flies, and humans.[28] At the time of filing, all of the computational tools for predicting miRs were based on a limited number of eukaryotic sequences (*i.e.*, worm, flies, vertebrates and plants). The existence of these eukaryotic sequence-based algorithms provided no guidance to one of ordinary skill in the art with regard to predictive algorithms for divergent single-celled organisms such as bacteria and yeast, or for acellular viruses.

Nevertheless, the Examiner asserts that Storz, G. (Science, 2002;296:1260-3) ("Storz") discloses that the bacterium *E. coli* was known at the time of filing to contain 50-200 non-coding

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[27] The Examiner has only provided prior art that demonstrates identification of miRNAs in a limited number of complex eukaryotes such as vertebrate (human, mice and rats), invertebrate animals (*C. elegans*, Drosophila, and plants) at the time of filing.

[28] As discussed in Appellant's office action response of March 16, 2009, miRseeker of Lai relies on miRNA sequences conserved across bilaterian evolutionary related species (*i.e.*, complex eukaryotes) to identify new miRNA sequences and precursors. *See* Lai at page 2, first column lines 7-12; at second column, lines 1 and 2 of second full paragraph; *and* at page 4, second column, first full paragraph. As concluded by Lai, "the approach used in this study should be applicable to the analysis of other sets of sequenced genomes of related higher eukaryotic model organisms." Lai at page 17, first column, second full paragraph, lines 11-13. Clearly, Lai is limited to the identification of miRNAs within a few small branches of the phylogenic tree–a limited number of complex eukaryotes such as vertebrate animals (humans, mice, and rats), invertebrate animals (*C. elegans*, Drosophila), and plants. While Lai disclose that computational method may be useful to identify new miRNAs in the genomes of highly related eukaryotes such as worms, flies, humans, and perhaps all animals, the cited references fail to state or demonstrate in any way that miRNAs were reasonably expected to be present in divergent, single-celled organisms such as bacteria or yeast, let alone viruses.

hairpin precursor-structured RNAs. The Examiner also asserts that this reference discloses that the use of computer-based searches for identifying non-coding RNAs in yeast, bacteria, and other single-celled organisms based on the properties of other known non-coding RNAs was routine. As an example, the Examiner cites Storz as allegedly equating the functions of small temporal RNAs from *C. elegans*, which are **not miRNAs**, to short RNAs from bacteria, because both types of RNAs repress mRNA translation and exhibit temporal expression. The Examiner thus concludes that in view of these teachings, and the disclosure of hairpin structures by Zhu, Ghringhelli, Baumstark, Ozdarendeli, Davison, Yu, Konings et al. (Journal of Virology, 1992), that there was no scientific reason for one to believe that miRNAs and miRNA hairpin precursors were exclusively present in complex eukaryotes.

But Storz has one glaring and fundamental omission—not once is a virus mentioned in all of Storz's discussion about the purportedly wide conservation of functional, noncoding RNAs. Instead, Storz focuses only on eukaryotic and other cellular organisms. With specific reference to miRNAs, Storz states, "[a]s yet there is no evidence of miRNAs in bacteria, archea, or fungi, but it might be fruitful to search for RNAs of <25 nt in these organisms."[29] Thus, even when Storz invites one of skill to look for miRNAs in other organisms based on the existence of miRNAs in complex eukaryotes, Storz notably omits viruses.

Storz's omission of viruses is not one of oversight. Rather, it reflects the lack of a reasonable expectation of success that one of ordinary skill in the art would have had in predicting virus genomes to contain miRNAs. The view reflected by Storz is entirely consistent with the sworn declaration of Dr. Alik Honigman that Appellant filed on February 26, 2008 (the "Honigman Declaration"). Dr. Honigman, an expert in microbiology with a substantial record of publishing scientific papers on viruses[30], states, "… although logically, from a functional point of view, one could have thought that viruses can benefit from miRNA, **I was skeptical that miRNAs existed in viruses**."[31] Dr. Honigman holds this view, even though, "[m]any secondary hairpin structures were known to exist in viruses."[32] He continues, "… however, each of these structures act in *cis*-related regulation… rather than *trans*-related regulation, such as a mRNA. For these reasons, I would

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[29] Storz at page 1261, column 1, line 14.

[30] *See* Honigman Declaration at Curriculum Vitae (disclosing a large number of publications in this area of research).

[31] Honigman Declaration at item 4 (emphasis added).

[32] Honigman Declaration at item 5.

have been skeptical that viruses contain miRNAs."[33] Dr. Honigman further points out that, "[i]n fact, in an estimation of the number of miRNAs in the human genome by one of the leaders in the miRNA field, Lim *et al.*, *Science* 299:1540 (2003) states the belief that miRNAs do not exist in more simple organisms such as yeast. Thus, at the filing date of this application, it was believed in the field that miRNAs did not exist in viruses."[34]

Consistent with Dr. Honigman's expert opinion of how the teachings in the art would have led one of skill to believe that viral genomes would not exist in simple organisms like viruses, Appellant has also presented evidence that viral genomes would be believed too small to contain miRNA hairpin precursors, based on the observed frequencies of miRNAs in eukaryotic genomes at the time of filing. Specifically, Appellant presented to the Examiner the following Tables 1 and 2, describing the numbers of known distinct miRNAs in various genomes, and the miRNA hairpin precursor frequencies in their respective genomes.[35] The tables below also show the predicted number of miRNA hairpin precursors in viruses, based on the known miRNA hairpin precursor frequencies in eukaryotes.

The critical point here is that these estimated frequencies in viruses are specifically based on the known numbers of miRNA hairpin precursors from eukaryotes, and **not** the number of generic hairpins. Appellant does not dispute the Examiner's assertion that hairpin structures were generally known in viruses at the time of filing–which is the foundation on which the Examiner's assertion of obviousness rests–but the Examiner consistently conflates hairpin structures from viruses that have nothing to do with miRNA hairpin precursors with the very specific miRNA hairpin precursors which form the basis of the predictions below. The Examiner's comparison of generic hairpin structures that were known in viruses to the very specific miRNA hairpin precursors that were known only in eukaryotes at the time of filing is one of apples to oranges. The only relevant consideration is what one of ordinary skill in the art would have predicted about the probability that specific, miRNA hairpin precursors were present in a viral genome, based on what was known about these specific types of hairpin precursors in eukaryotes. That is what one of skill would have focused on in making a prediction, and that is what Appellant presents in the tables below.

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[33] Honigman Declaration at item 5.

[34] Honigman Declaration at item 6.

[35] The numbers of miRNAs were known at the time of filing through the available Sanger miRNA database available at the time of filing, which was Revision 7 (available at www.mirbase.org/ftp.shtml, last accessed on January 18, 2011).

Table 1 describes the frequencies of known unique miRNA hairpin precursors in the genomes of various eukaryotes at the time of filing.

Table 1 – Frequency of Known miRNA Hairpin Precursors in the Genome

Organism	Genome Size (bp)	Known Distinct miRNA Hairpins	bp/miRNA Hairpin
Vertebrate			
Human	2.9×10^9	176	1.65×10^7
Rat	2.75×10^9	38	7.24×10^7
Mouse	2.64×10^9	202	1.31×10^7
Invertebrate			
C. elegans	1.0×10^8	106	9.43×10^5
Drosophila melanogaster	1.2×10^8	78	1.54×10^6
Plant			
Arabidopsis thaliana	1.57×10^8	43	3.65×10^6
Average			1.80×10^7

This table reveals that, on average, one miRNA hairpin precursor occurs every 1.80×10^7 bp. The highest frequency, based on *C. elegans*, is one miRNA hairpin precursor for every 9.43×10^5 bp, and the lowest, based on rat, is one per 7.24×10^7 bp.

If the lowest and highest frequencies known from eukaryotes at the time of filing are applied to virus genomes of various sizes, even the largest virus would not be expected to have even one miRNA hairpin precursor. This is because the predicted frequency of miRNA hairpin precursors in the largest virus genome (human cytomegalovirus ("HCMV")) based on the highest known frequency of miRNA hairpin precursors from a eukaryote (*C. elegans*) would be 0.243, or less than one.[36] This conclusion is illustrated in the following table.

Table 2 – Predicted miRNA Hairpin Precursors in Viruses[37]

Organism	Genome Size (bp)	Expected miRNA Hairpins Based on Average Frequency in Eukaryotes	Expected miRNA Hairpins Based on Highest Frequency in Eukaryotes
Virus			
Epstein Barr Virus	1.75×10^5	0.0972	0.186
HCMV	2.30×10^5	0.0128	**0.243**
HPV	7.91×10^3	0.000439	0.00839
HSV-1	1.52×10^5	0.00844	0.161

[36] *See* bold underline text in Table 2 herein.

[37] The average frequency of known hairpins at the time of filing was 1 hairpin for every 1.80×10^7 bp, as discussed in greater detail in Appellant's office action reply of February 26, 2008. The highest hairpin frequency Appellant presented in the office action reply of February 26, 2008 was 1 hairpin for every 9.43×10^5 bps in *C. elegans*.

A shown in the right-hand column of Table 2, none of the viral genomes are expected to contain a single miRNA hairpin precurosor. Nevertheless, the Examiner asserts that the numbers used by Appellant to illustrate predicted miRNA hairpin precursor frequencies cannot be believed. In particular, the Examiner disputes Appellant's numbers by citing that other references that had been published at the time of filing and that allegedly disclose higher numbers of predicted miRNA hairpin precursors in eukaryotes. For example, the Examiner asserts that the Lai discloses that nearly 1% of the human genome is predicted miRNA genes. This assertion inaccurately describes Lai's teaching. What Lai actually discloses is, "[t]he results of our studies are most similar to analyses by Bartel and colleagues predicting 200-255 miRNA genes in vertebrates, or **nearly 1% of the predicted genes** in humans [citation omitted]; this is comparable to our estimate of flies."[38] Lai's upper limit of 255 human miRNAs is not substantively different from Appellant's asserted 176 unique human miRNA hairpin precursors known from the Sanger miRNA database at the time of filing. Importantly, even if Lai's estimate is more accurate, the miRNA hairpin frequency in humans based on Lai would be one for every 1.14×10^7 bp, which is still lower than *C. elegans*, and therefore does not change the conclusion from Table 2 above, based on applying the highest-known frequency (i.e., the best case scenario for the Examiner) from *C. elegans* to the largest viral genome size of HCMV.

The Examiner also disputes Appellant's estimates of predicted viral miRNA hairpin precursors by citing Grad *et al.* (Molecular Cell, 2003) ("Grad") as allegedly disclosing that, rather than the 106 unique miRNAs known from Sanger as shown in Table 1, the *C. elegans* genome was estimated at the time of filing to have contained as many as 300 miRNAs. Again, assuming the Examiner is correct, this still does not change the fact that even the largest viral genome would not have been predicted to contain a single miRNA hairpin precursor. Taking the Examiner's assertion at face value, this would mean that one of ordinary skill in the art would have predicted the existence of one miRNA hairpin precursor for every 3.33×10^5 bp of the *C. elegans* genome.[39] Based on this frequency, the Epstein Barr Virus genome would have been predicted to contain 0.691 miRNA hairpin precursors, rather than Appellant's previously-asserted frequency of 0.243 in Table 2 above.[40]

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[38] Lai at page 16, column 1, line 48 (emphasis added).

[39] This is derived by dividing the size of the *C. elegans* genome of 1.8×10^8 bp, which the Examiner does not dispute, by the Examiner's asserted 300 estimated miRNAs in the *C. elegans* genome based on Grad.

[40] This is derived by multiplying the estimate of 1 miRNA hairpin precursor per 3.33×10^5 bp from *C. elegans* by the 2.3×10^5 bp genome size of HCMV.

That is, even accepting the Examiner's most generous prediction for the highest known miRNA hairpin precursor frequency in any known genome at the time of filing, and applying it to the largest known viral genome–thereby providing the highest probability of harboring a miRNA hairpin precursor–one of skill still would have predicted that no virus genome contains a miRNA hairpin precursor. This is especially so, given that most viral genomes, including HSV-1, are considerably smaller than the genome of HCMV.

Despite this prediction, the Examiner asserts that there is plenty of intergenic space in HSV-1 genomic sequence for predicting the existence of miRNA hairpin precursors. The Examiner cites Perry to support the assertion that a virus such as HSV-1 contains sufficient length and space of nucleotide sequences to harbor hairpin precursors. Appellant respectfully submits that with regard to the Examiner's assertion, the frequency of predicted hairpins based on the models available at the time of filing would have predicted a frequency of less than one for HSV-1 as well.

HSV-1 is a double stranded DNA genome of 152,000 bp.[41] Thus, the HSV-1 genome is nearly the same size as that of Epstein Barr Virus. As shown above in Table 2, and as Appellant previously showed in the office action response of February 26, 2008, the estimated miRNA hairpin precursor frequency for the Epstein Barr Virus genome would have been, 0.186, or less than one. Even using the Examiner's asserted *C. elegans* frequency, the frequency for Epstein Barr virus would be 0.526, or still less than one.[42] Additionally, applying the Examiner's more generous frequency from *C. elegans* to the size of the HSV-1 genome specifically cited by the Examiner, the predicted frequency of miRNA hairpin precursors for HSV-1 would be 0.457, which is also less than one. Furthermore, the viruses of Zhu, Ghiringhelli, Baumstark, Ozdarendeli, and Davison are similarly-sized to the viruses listed in Table 2 above. Consequently, these other cited viral genomes would similarly have the same predicted miRNA hairpin precursor frequency of less than one.

Appellant's predictions are entirely consistent with the expert opinion of Dr. Honigman. In particular, he states,

> ***"[a]t the time [of filing], miRNAs were believed to be extremely rare within the large genomes of complex eukaryotes. At comparable prevalence within the genome or non-coding***

[41] See Perry at page 1.

[42] It would be 0.526, based on multiplying the 1 miRNA hairpin precursor frequency per 3.33×10^5 of *C. elegans* genome by the 1.75×10^5 bp genome size of Epstein Barr Virus.

> ***sequences, miRNAs would not be present in a virus because a viral genome and viral non-coding sequences are on the order of 103 to 106 times smaller than the complex multicellular eukaryotes that were known to contain miRNAs.***[43]

Thus, one of ordinary skill in the art, even when faced with the teachings of the cited viral hairpin-related references cited by the Examiner, one of ordinary skill in the art would not reasonably expect any viral genome to contain a miRNA hairpin precursor. Appellant reiterates that notwithstanding the Examiner's assertion that Appellant's numbers in the tables above are not to be believed, the bottom line is that even using the Examiner's asserted miRNA hairpin precursor frequency from *C. elegans*, which is only about three times higher than Appellant's, this unreasonable expectation of success is not altered. That is because one of skill still would not have had a reasonable expectation of finding a miRNA hairpin precursor in even the largest viral genome, let alone that of HSV-1. The teachings of Perry on the HSV-1 genome do not dispel this notion.

Accordingly, the Examiner has failed to provide any concrete evidence that one of ordinary skill in the art would reasonably have bridged the phylogenic gap between the cited prior art's identification of miRNAs within a few small branches of the phylogenic tree that were limited to eukaryotes, and the far more distant branches of the phylogenic tree representing single-celled organisms such as bacteria and yeast, and acellular organisms such as viruses. Further, just because viruses may have intergenic spaces as argued by the Examiner, this knowledge by no means overcomes the fact that one of ordinary skill in the art would reasonably have predicted that even the largest viral genome would have contained less than 1 miRNA hairpin precursors. Appellant additionally submits that the Examiner has failed to give proper weight to Appellant's proffered evidence of unexpected results.

In particular, six months after the filing date of the instant application, the existence of viral miRNAs was reported by Pfeffer *et al.* (*Science*, 2004;304:734-6). Consideration of the circumstances surrounding the Pfeffer publication indicate that the consensus in the art at this time was that the discovery of viral miRNA was ground breaking, and therefore unexpected.[44] The *Science* Commentary reports that, "miRNAs had previously been found only in the genomes of plants and

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[43] Honigman Declaration at item 4.

[44] *See e.g.*, the commentary in *Science*, 2004;304:645-8 (the "Science Commentary").

animals, each of which are complex eukaryotes. Pfeffer *et al* show the presence of miRNA in a virus, the '**fourth domain**' of life."[45] The use of the words "fourth domain" reflects the view in the art that viruses and other major branches of the evolutionary tree, including eukaryotes, were separated by a large evolutionary distance. Because of this large separation, one of ordinary skill in the art would not have reasonably expected viruses to contain miRNAs, and this explains why the discovery of miRNAs in viruses was such a surprise to the scientific community, warranting a separate editorial commentary in Science. As Dr. Honigman states, "Pfeffer *et al.* was clearly regarded as a significant advance by the scientific community as shown by being published in *Science* and by also meriting a comment in Editor's Choice of *Science*. The editorial comment in *Science* brings attention to the discovery of miRNAs in the 'fourth domain of life,' indicating that this was recognized as a ground breaking achievement."[46] Consistent with Appellant's evidence described above, Dr. Honigman concludes,

> ***[i]n accordance with my experience in this field and my knowledge of the state of the art at the time of the invention of this application was made, it is clear that the inventors broke with the established teachings in the field to identify miRNAs in simple organisms using computational approaches not requiring sequence conservation. I regard this as a significant advance in the field.***[47]

In summary, in view of (1) the fact that miRNAs had only been isolated from species that are clustered within one region of the phylogenic tree completely divergent from viruses; (2) the lack of predictive miRNA algorithm tools to account for viral genomic sequences; (3) doubts regarding the frequency of miRNA hairpin precursors in viruses, given the lack of sufficient genome size of viruses necessary to harbor miRNA hairpin precursors; and (4) the ground breaking and unexpected nature of Appellant's discovery of miRNAs in viruses, one of skill would not reasonably have predicted the claimed invention, or have expected to succeed in identifying viral miRNA hairpin precursors at the time of filing. Based on the evidence above and the inability of the Examiner to

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[45] *See* the Science Commentary at page 648 (emphasis added).

[46] Honigman Declaration at item 7.

[47] Honigman Declaration at item 8.

counter this evidence, Appellant has shown that there was no reasonable expectation by one of ordinary skill in the art at the time of filing that miRNAs would be present in the viral genome. Appellant's extensive record as discussed above demonstrates this unpredictability. In view of the foregoing, the Appellant respectfully asserts that one of skill would not have expected to be able to identify the claimed viral nucleic acids. Accordingly, Appellant submits that the rejection of claims 21-34, 50, 52, and 53 under 35 U.S.C. § 103(a) over Lai in view of Zhu, Ghiringhelli, Baumstark, Ozdarendeli, Davison, and Perry has been overcome and should be withdrawn.

E. The rejection of claims 21, 33-34, 52 and 53 are on grounds of nonstatutory obviousness-type double patenting has been overcome because of previously filed terminal disclaimers.

Claims 21, 33-34, 52 and 53 stand rejected on the grounds of nonstatutory obviousness-type double patenting over various claims of U.S. Patent No. 7,696,334 (U.S. Patent Appl. No. 10/604,942), U.S. Patent No. 7,790,867 (U.S. Patent Appl. No. 10/604,943), U.S. Patent No. 7,696,342 (U.S. Patent Appl. No. 10/604,945), U.S. Patent No. 7,759,478 (U.S. Patent Appl. No. 10/604,984), U.S. Patent No. 7,217,807 (U.S. Patent Appl. No. 10/604,944) , U.S. Patent Appl. Nos. 10/709,739 (now U.S. Patent No. 7,777,022), 11/511,035 (now U.S. Patent No. 7,795,419), and 12/517,760. The instant application and each of the cited references are commonly owned by Rosetta Genomics, Inc. Applicant previously submitted a terminal disclaimer in compliance with 37 C.F.R. §1.321(c) and 37 C.F.R. §3.73(b) for each of the cited patent applications and patents, thereby overcoming the alleged nonstatutory double patenting rejection. Accordingly, Applicant submits that the nonstatutory obviousness-type double patenting rejection of claims 21, 33, 34, 52 and 53 have been overcome.

VIII. CONCLUSION

For the reasons stated above, the rejections involving claims 3, 32-35, and 49 should be withdrawn.

Respectfully submitted,

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Dated:

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CLAIMS

1. - 20 (Canceled)

21. (Rejected) An isolated first viral nucleic acid or complement thereof, wherein

(a) the first viral nucleic acid consists of 15-24 nucleotides;

(b) a second viral nucleic acid consisting of 50 to 131 nucleotides comprises the first viral nucleic acid;

(c) the second viral nucleic acid is capable of forming a hairpin, wherein

(i) the hairpin comprises two stem segments and an intervening loop segment;

(ii) the two stem segments each consists of 14-71 nucleotides;

(iii) the loop segment consists of 3 to 19 nucleotides;

(iv) the first and second stem segments are at least 30.8% complementary; and

(v) one of the stem segments of the hairpin comprises the first viral nucleic acid,

(d) the first viral nucleic acid is capable of binding to a binding site of a mRNA; and

(e) the first viral nucleic acid is capable of inhibiting expression of a protein encoded by a mRNA, wherein the mRNA comprises the binding site;

wherein a viral genome comprises the sequence of the first and second viral nucleic acids.

22. (Rejected) The nucleic acid of claim 21, wherein the first viral nucleic acid is at least 40.9% complementary to the mRNA.

23. (Rejected) The nucleic acid of claim 21, wherein the untranslated region of the mRNA comprises the binding site.

24. (Rejected) The nucleic acid of claim 21, wherein the hairpin is characterized by a negative free energy of folding of at least –1.8 Kcal/mol.

25. (Rejected) The nucleic acid of claim 21, wherein the mRNA is transcribed from the genome of the host of the virus.

26. (Rejected) The nucleic acid of claim 21, wherein the first viral nucleic acid and the mRNA are in different parts of a genome.

27. (Rejected) The nucleic acid of claim 21, wherein the viral nucleic acid is from a DNA virus.

28. (Rejected) The nucleic acid of claim 27, wherein the virus is selected from the group consisting of: human adenovirus, adeno-associated virus, B19 virus, human herpesvirus, human papillomavirus, molluscum contagiosum virus, ovine adenovirus, rat cytomegalovirus, vaccinia virus and variola virus.

29. (Rejected) The nucleic acid of claim 21, wherein the viral nucleic acid is from a RNA virus.

30. (Rejected) The nucleic acid of claim 29, wherein the virus is selected from the group consisting of: Barmah forest virus, Borna disease virus, bovine kobuvirus, Colorado tick fever virus, dengue virus, Eastern equine encephalitis virus, Encephalomyocarditis virus, equine rhinovirus, hepatitis virus, human astrovirus, human coronavirus, human echovirus, human enterovirus, human metapneumovirus, human parainfluenza virus, human respiratory syncytial virus, human rhinovirus, influenza virus, Japanese encephalitis virus, Marburg virus, measles virus, Murray valley encephalitis virus, Norwalk virus, poliovirus, respiratory syncytial virus, reston Ebola virus, rubella virus, salmon pancreas disease virus, SARS coronavirus, simian picornavirus 1, Sindbis virus, sleeping disease virus, tick-borne encephalitis virus, transmissible gastroenteritis virus, West Nile virus, Western equine encephalomyelitis virus, Yellow Fever virus and Zaire Ebola virus.

31. (Rejected) The nucleic acid of claim 29, wherein the viral nucleic acid is a retrovirus.

32. (Rejected) The nucleic acid of claim 31, wherein the virus is selected from the group consisting of: human immunodeficiency virus 1, human immunodeficiency virus 2, human T-lymphotropic virus 2 and simian immunodeficiency virus.

33. (Rejected) A probe comprising a nucleic acid according to any one of claims 21-32.

34. (Rejected) A vector comprising a nucleic acid according to any one of claims 21-32.

35. (Withdrawn) An isolated first viral nucleic acid or complement thereof, wherein

(a) the first viral nucleic acid consists of 50 to 131 nucleotides and comprises a second viral nucleic acid;

(b) the second viral nucleic acid consists of 15-24 nucleotides;

(c) the first viral nucleic acid is capable of forming a hairpin, wherein

(i) the hairpin comprises two stem segments and an intervening loop segment;

(ii) the two stem segments each consist of 14-71 nucleotides;

(iii) the loop segment consists of 3 to 19 nucleotides;

(iv) the first and second stem segment are at least 30.8% complementary; and

(v) one of the stem segments of the hairpin comprises the second viral nucleic acid,

(d) the second viral nucleic acid is capable of binding to a binding site of a mRNA; and

(e) the second viral nucleic acid is capable of inhibiting expression of a protein encoded by a mRNA, wherein the mRNA comprises the binding site;

wherein a viral genome comprises the sequence of the first and second viral nucleic acids.

36. (Withdrawn) The nucleic acid of claim 35, wherein the second viral nucleic acid is at least 40.9% complementary to the mRNA.

37. (Withdrawn) The nucleic acid of claim 35, wherein the untranslated region of the mRNA comprises the binding site.

38. (Withdrawn) The nucleic acid of claim 35, wherein the hairpin is characterized by a negative free energy of folding of at least –1.8 Kcal/mol.

39. (Withdrawn) The nucleic acid of claim 35, wherein the mRNA is transcribed from the genome of the host of the virus.

40. (Withdrawn) The nucleic acid of claim 35, wherein the second viral nucleic acid and the mRNA are in different parts of a genome.

41. (Withdrawn) The nucleic acid of claim 35, wherein the viral nucleic acid is from a DNA virus.

42. (Withdrawn) The nucleic acid of claim 41, wherein the virus is selected from the group consisting of: human adenovirus, adeno-associated virus, B19 virus, human herpesvirus, human papillomavirus, molluscum contagiosum virus, ovine adenovirus, rat cytomegalovirus, vaccinia virus and variola virus.

43. (Withdrawn) The nucleic acid of claim 35, wherein the viral nucleic acid is from a RNA virus.

44. (Withdrawn) The nucleic acid of claim 43, wherein the virus is selected from the group consisting of: Barmah forest virus, Borna disease virus, bovine kobuvirus, Colorado tick fever virus, dengue virus, Eastern equine encephalitis virus, Encephalomyocarditis virus, equine rhinovirus, hepatitis virus, human astrovirus, human coronavirus, human echovirus, human enterovirus, human

metapneumovirus, human parainfluenza virus, human respiratory syncytial virus, human rhinovirus, influenza virus, Japanese encephalitis virus, Marburg virus, measles virus, Murray valley encephalitis virus, Norwalk virus, poliovirus, respiratory syncytial virus, reston Ebola virus, rubella virus, salmon pancreas disease virus, SARS coronavirus, simian picornavirus 1, Sindbis virus, sleeping disease virus, tick-borne encephalitis virus, transmissible gastroenteritis virus, West Nile virus, Western equine encephalomyelitis virus, Yellow Fever virus and Zaire Ebola virus.

45. (Withdrawn) The nucleic acid of claim 43, wherein the viral nucleic acid is a retrovirus.

46. (Withdrawn) The nucleic acid of claim 45, wherein the virus is selected from the group consisting of: human immunodeficiency virus 1, human immunodeficiency virus 2, human T-lymphotropic virus 2 and simian immunodeficiency virus.

47. (Withdrawn) A probe comprising a nucleic acid according to any one of claims 35-46.

48. (Withdrawn) A vector comprising a nucleic acid according to any one of claims 35-46.

49. (Canceled)

50. (Rejected) The nucleic acid of claim 21, wherein the first viral nucleic acid comprises a sequence as set forth in any one of SEQ ID NOs: 1,557-3,353, or a complement thereof.

51. (Withdrawn) The nucleic acid of claim 35, wherein the first viral nucleic acid comprises a sequence as set forth in any one of SEQ ID NOs: 1-1,556, or a complement thereof.

52. (Rejected) The nucleic acid of claim 21, wherein the first viral nucleic acid consists of 18 to 24 nucleotides in length.

53. (Rejected) The nucleic acid of claim 21, wherein the second viral nucleic acid consists of 50 to 120 nucleotides in length.

54. (Withdrawn) The nucleic acid of claim 35, wherein the second viral nucleic acid consists of 18 to 24 nucleotides in length.

55. (Withdrawn) The nucleic acid of claim 35, wherein the first viral nucleic acid consists of 50 to 120 nucleotides in length.

EVIDENCE APPENDIX

1. Declaration of Dr. Alik Honigman under 37 C.F.R. § 1.132. This declaration was filed on February 26, 2008, and the Examiner considered it in the non-final office action mailed on September 16, 2008. The Examiner's acknowledgment and consideration of the declaration is found at page 3, line 12 of the February 26, 2008 office action.

RELATED PROCEEDINGS APPENDIX

None